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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/917,858	07/31/2001	Regina Geertruida Schoemaker	147/50194	9455

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EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 03/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/917,858	SCHOEMAKER, REGINA GEERTRUIDA	
	Examiner	Art Unit	
	Lakshmi S Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of request for continued examination and declaration dated 12-12-03 is acknowledged. Claims 1-5 are pending.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-12-03 has been entered.

The following is a new rejection:

Claim Rejections - 35 USC § 103

1. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lepran et al (J. cardiovascular Pharmacology, 1994, submitted on PTO-1449).

Instant claims 1-5 are directed to a method of treating a patient who has suffered a myocardial infarction, comprising administering 4-chloro-5-[(4,5-dihydro-1H-imidazol-2-yl)-amino]-6-methoxy-2-methylpyrimidine, effective to inhibit or treat myocardial damage

secondary to myocardial infarction, for postmyocardial infarction management and promoting recovery or rehabilitation of myocardial status.

Lepran et al teach that increased sympathomimetic activity seen during the acute phase of myocardial infarction aggravates arrhythmias, frequently leading to life threatening ventricular fibrillation (Introduction on page S9). Lepran et al studied the effect of moxonidine on arrhythmias induced by myocardial infarction in rats and observed that moxonidine significantly decreases the incidence of ventricular tachycardia during the first 15 minutes of infarction, decreased the infarct size and the number of animals survived without developing any arrhythmias was significantly increased (page S11, col. 2). Lepran et al further teach that moxonidine at 0.03 mg/kg and 0.1 mg/kg is also effective in preventing reperfusion-induced arrhythmias after myocardiac ischemia (S11, col. 2).

Lepran et al does not explicitly state "postmyocardial management or recovery or rehabilitation". However, Lepran et al clearly state that arrhythmias and life-threatening ventricular fibrillation are caused due to increased sympathomimetic activity during the acute phase of myocardial infarction. In other words, Lepran et al aims at arrhythmias occurred after myocardial infarction. Therefore, it is implicit in the teachings of Lepran et al that moxonidine is administered to treat or inhibit the damage (arrhythmias or ventricular fibrillation) resulting from myocardial infarction (i.e., secondary to myocardial infarction or postmyocardial infarction). Lepran et al teaches that moxonidine is dissolved in saline, which reads on the instant carrier (claim 5). Examiner notes that instant application describes that moxonidine treatment is suitable to man and large animals (page 2, last paragraph) and experiments were performed on

rats (pages 7-13). Accordingly, the instant term "patients" encompass rats, which are also used in the experiments of Lepran et al.

The following rejection of record has been maintained:

2. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/46241 (submitted on PTO-1449, referred to as WO '241).

Instant claims are directed to a method treating a patient who has suffered a myocardial infarction by administering moxonidine effective for inhibiting/treating the secondary damage to myocardial infarction, effective to recover myocardial status and postmyocardial management.

WO '241 discloses a method of treating congestive heart failure by administering moxonidine (abstract, page 1, lines 10-15, page 13, lines 1-13, page 18, lines 14-22, page 19, lines 12-24). Examiner notes that the compound of the instant claims is also known as moxonidine (as described on page 1 of the specification). WO '241 disclose that moxonidine, a well tolerated anti-hypertensive drug (page 8, lines 16-29), reduces blood pressure and induce regression of left ventricular hypertrophy (page 9, lines 30 through page 10, lines). WO '241 further discloses that moxonidine treatment reduces vascular resistance while increasing cardiac output (page 10, lines 24-29).

WO '241 does not explicitly state postmyocardial infarction or recovery of myocardial status, as claimed. However, WO '241 discloses that congestive heart failure (CHF) is the end result of long-term or severe cardiac deficits, often caused by long-standing hypertension, acute myocardial infarction, idiopathic cardiomyopathy and a wide variety of secondary insults (page 1, lines 22-26). Further, WO '241 disclose that cardiac and peripheral regulatory mechanisms

such as increased heart rate, hypertrophy, increased sympathetic nervous stimulation etc., play a role early in CHF, which further contributes to myocyte necrosis, hypertrophy leading to increased myocardial remodeling and heart failure (page 1, lines 29 through page 3, line 36 and page 4, lines12-14). Examiner notes that same regulatory mechanisms are also observed in postmyocardial infarction patients (pages 3-5 of the instant application) as those described by WO '241. Therefore, moxonidine treatment of CHF taught by WO '241 reads on the instant treatment of postmyocardial infarction or myocardial damage secondary to myocardial infarction. Further, WO '241 shows that moxonidine induces regression of myocardial hypertrophy, which often proceeds heart failure, by decreasing blood pressure and reducing the thickness of left ventricular septal thickness (paragraph bridging pages 8 and 9) and increases cardiac output by reducing vascular resistance (page 10, lines 24-29).

Therefore, it would have been obvious for one of an ordinary skill at the time of the instant invention that moxonidine treatment taught by WO '241 would be effective in inhibiting or treating the damages secondary to myocardial infarction, in postmyocardial management and in recovering myocardial status because WO '241 teaches that conditions such as congestive heart failure and myocardial hypertrophy occur after myocardial infarction i.e., secondary damage or postmyocardial condition. Therefore, one of an ordinary skill in the art would have administered moxonidine to patients suffered from myocardial infarction with an expectation to treat or manage the conditions after myocardial infarction such as heart failure, myocardial hypertrophy due to reduced hypertension, regressed ventricular septal thickness and increased cardiac output i.e., recovering myocardial condition.

Response to Arguments

Applicant's arguments filed 9-9-02 have been fully considered but they are not persuasive. Examiner also considered the declaration, submitted under 37 CFR 1.132, by applicants and the arguments presented therein. In response to applicants' arguments and the declaration, examiner has withdrawn the previous rejection of claims 1-5 as being anticipated by WO '241 or by Lepran et al.

WO '241:

Applicants argue that is limited to the use of moxonidine in the form of a "non-immediate release" composition for the treatment of congestive heart failure (CHF) and only refers to hemodynamic parameters, which is not the focus of the claimed invention. Applicants also argue that WO '241, makes no reference to treatments for postmyocardial infarction (PMI) or recovery of myocardial status, and only relates to treatment of CHF. Applicants further argue that, as explained in the declaration of Dr. Rupp, the treatments for CHF are targeted at improving the functioning of the heart (cardiac functioning), which is different from MI (which is preserving ischemic myocardium and inhibiting necrosis). However, this argument is not persuasive because instant claims are directed to treating a patient "who has suffered a myocardial infarction", effective to inhibit the myocardial damage secondary to myocardial infarction. In other words, the treatment includes events or conditions subsequent to myocardial infarction, which cause further myocardial damage. Claims do not specifically state any particular event. Further, instant specification recites that in post-infarction patients with lysis, treatment with compounds used according to the invention also prevents development of myocardial heart failure; and that those without lysis pass into chronic phase of myocardial infarction where

sympathetic nervous system plays a role eventually in the development of heart failure (pages 3-4). Thus, both instant application as well as WO '241 states that CHF is caused by after or as a result of myocardial infarction (MI). Further, WO '241 also states a chronic CHF leads to activation of neurohormonal systems, which leads to increased cardiac rate, myocyte necrosis and hypertrophy, which in turn leads to myocardial remodeling. Thus, WO '241 clearly aims at all the events that are post-myocardial infarction, which include secondary myocardial damage and is thus suggestive of reduced myocardial damage. Although applicants have argued that WO '241 only teaches hemodynamic changes, the reference does teach how these are further linked to increased cardiac rate, myocyte necrosis and hypertrophy i.e., myocardial conditions; all of which are also described in the specification. Emphasis is added on the specific statement that " a desirable strategy for the management of MI patients, especially also with the aim of preventing the progression of heart failure after MI".

Applicants refer to the explanation of Dr. Rupp in the declaration and argue that CHF may be caused by a variety of mechanisms or conditions and that just as it is improper to assume that a treatment for CHF is suitable for treating all of the mechanisms and conditions that may precede CHF, it is similarly improper to assume that the method of treating CHF taught by WO '241 is beneficial in treating PMI. Applicants argue that WO '241 is only aimed at improving heart conditions and that there is no suggestion or motivation for a skilled artisan to inhibit myocardial damage following MI. However, applicants arguments are not persuasive because in the instant case, "PMI" is not disease by itself and instead is a condition or conditions resulting from MI, which as admitted by applicants includes myocardial heart failure, or sympathetic nervous system induced cardiac out put, hypertrophy that in turn lead to unfavorable heart rate

and heart failure. WO '241 (on page 4) established a clear correlation between cardiac out put and contractile state of heart that is controlled by sympathetic nervous system and that moxonidine is efficient in regressing myocardial hypertrophy. Accordingly, CHF patients of WO '241 belong to the claimed category of "patients who suffered myocardial infarction". With respect to the dosage, WO '241 also states an amount effective to diminish or relieve one or more conditions associated with CHF, thus, including the myocardial conditions.

Lepran:

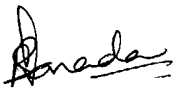
Applicants argue that Lepran article is limited to describing the effects of moxonidine on arrhythmias induced by myocardial ischemia or reperfusion in an animal model. Applicants argue that article teaches abnormal heart operation but not PMI damage or recover myocardial status that is different from arrhythmias or ventricular fibrillation. However, instant post-myocardial conditions do not distinguish from the conditions of Lepran. Further, applicants did not explain how they are different. Whereas, Lepran clearly states that moxonidine effectively reduces the arrhythmia caused by acute myocardial infarction. Based on the declaration of dr. Rupp, applicants argue that Lepran rely on administering moxonidine before coronary ligation leading to whether MI or myocardial ischemia, whereas instant application claims recite post myocardial events. Applicants also argue that the teaching of Lepran may be useful if administered so that it is present during acute MI (during evolving MI), but not MI to prevent myocardial damage. Applicants' arguments have been considered but not found persuasive because applicants have not shown any difference in administering moxonidine before/during the MI or after MI or that benefits of administering moxonidine after MI. On the other hand, Lepran article suggests that administering moxonidine before coronary ligation or during MI would be

beneficial in preventing the sympathomimetic activity that may occur during acute MI that may aggravate arrhythmias. Accordingly, one of an ordinary skill in the art would have expected to prevent as well as inhibit the development of myocardial damage by administering moxonidine. This is also supported by the conclusion provided by Lepran, where it is stated that moxonidine effectively reduced the incidence of arrhythmias during the acute phase of MI. Therfore, it is examiner's position that administering moxonidine to patients who suffered from MI with an expectation to prevent conditions post MI such as arrhythmias would have been obvious for one of an ordinary skill in the art because admittedly the activated sympathomimetic nervous system in post MI patients increases myocardial contractility and also increases the development of life-threatening arrhythmias.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 7.30 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Lakshmi S Channavajjala
Examiner
Art Unit 1615
March 16, 2004